REMARKS

Status of the claims

Claims 24-32 and 34-38 are pending in the application.

Rejections under 35 U.S.C.§103

1) Nagaoka '615 (claims 24, 25 and 35-38) and *Nagaoka '330 (claims 24-27, 30–32 and 34-38)*

Claims 24, 25, and 35-38 remain rejected under 35 U.S.C.§103 as being obvious over Nagaoka '615.

a) Nagaoka '615 - The Examiner asserts that Nagaoka '615 teaches at column 1, lines 30-44 that "their *Lentinus edodes* (shiitake) mycelium extract is effective as an anti-tumor agent...." Applicants traverse this rejection and withdrawal thereof is respectfully requested. In the response of June 5, 2006 Applicants asserted, in part, that there is no disclosure in Nagaoka '615 of the inventive extract of the reference having activity as an anti-tumor agent and that the reference to an anti-cancer activity is with reference to JP 46859/1979, discussed in the BACKGROUND OF THE INVENTION. The Examiner disagrees with Applicant's interpretation of Nagaoka '615 and asserts that when the reference states "The effect of the bagasse of the culture medium used in this method is described..." (column 1, lines 30-31) the reference is discussing the inventive extract.

Applicants respectfully disagree with the Examiner's interpretation of the disclosure in Nagaoka '615. A grammatical parsing of the disclosure Nagaoka '615 from column 1, lines 22-31 clearly shows that "this" in line 31 refers to the JP 46859/1979. Column 1, lines 22-29 state,

> For example, Japanese Patent Laid-Open Publication No. 46859/1979 discloses a method for preparing a healthful food comprising the steps of inoculating basidiomycetes in a culture medium mainly composed of bagasse, proliferating the mycelium and squeezing the culture medium containing proliferated mycelium to obtain active ingredients.

The next sentence states, "The effect of the bagasse of the culture medium in this method..." *(emphasis added)* Grammatically, "this" is used in such a context to refer to the immediately aforementioned item, i.e. the method and culture medium disclosed in JP 46859/1979, not the inventive subject matter of Nagaoka '615, which is not discussed in the BACKGROUND OF THE INVENTION until line 50.

Thus, when Nagaoka '615 refers to "this method", the inventors of Nagaoka '615 are referring to the extraction methods of JP 46859/1979 discussed in the preceding paragraph. Applicants' interpretation is further supported by the discussion in column 1, lines 45-49, of Nagaoka '615, wherein it is stated that "In the method described in the above publication, however, there is a problem...." Thus, it is clear that when Nagaoka '615 state "this method" in column 1, line 30 they are referring to the method of the prior art. As such, there is no disclosure in Nagaoka '615 of a showing of antitumor activity associated with the preparation of Nagaoka '615.

On page 7 of the final office action, the Examiner addresses Applicants' arguments regarding the use of specific enzymes to prepare the extract of the invention. The Examiner asserts that one skilled in the art would expect that the use of any of the enzymes of Nagaoka '615 would result in an anti-tumor composition. Applicants disagree with this conclusion by the Examiner, in as much as different enzymes result in different digestion products having different activities.

The instant claims recite that the enzyme is cellulase, protease and/or glucosidase. Column 6, lines 35-36 recite using cellulase, protease, β-1,3-glucanase and chitinase. Nagaoka '615 further state that it is preferred that β-1,3-glucanase be present as the main component. See also the Abstract of Nagaoka '615, which states that "Useful ingredients are extracted from a

mycelium-containing culture medium by the steps of...separately, adding water and beta-1,3, glucanase and at least one enzyme selected from the group consisting of....." Thus, one skilled in the art would interpret Nagaoka '615 as requiring digestion with β-1,3-glucanase. The purpose of using β-1,3-glucanase in Nagaoka '615 is to obtain a product containing high levels of β-glucan. See the Abstract and column 4, lines 32-55. Nagaoka '615 further teach that the β-glucan is the component responsible for the postulated, but not shown, antitumor activity. Thus, one skilled in the art would conclude from the teachings of Nagaoka '615 that β-glucan is an essential component for antitumor activity.

The presently claimed method uses a preparation digested with cellulase, protease and glucosidase, i.e. no β-1,3-glucanase. Concomitant with the absence of β-1,3-glucanase in the digestion of the preparation of the invention, the resultant composition of the method of claim 1 contains only negligible levels of β-glucan (0.0037%). Nagaoka '615 teaches that β-glucan is the active component of the extract of the reference. One skilled in the art would not have any motivation to modify the reference teachings in a way that results in an extract that does not have the active component. In fact, one would be lead to conclude that such a modification would render the prior art extract ineffectual.

The instant invention, however, unlike Nagaoka '615 does not rely on β-glucan for activity. β-glucan is believed to have anti-tumor effects through the activation of a humoral (i.e. B cell-mediated) immune response. The instant method on the other hand, is specifically limited to γδT cell activity, i.e. a specific T-cell population mediated immune response.

As such, one skilled in the art would not be motivated to modify Nagaoka '615 by omitting digestion with β-1,3-glucanase and thereby having a composition that contains only negligible β-glucan. "If proposed modification would render the prior art invention being

modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)" MPEP §2143.01. Modification of Nagaoka '615 needed to achieve the invention, i.e. omission of digestion with β-1,3-glucanase, would render the extract of Nagaoka '615 unsatisfactory for its intended purpose because such a modification would result in an extract having effectively no β-glucan, which Nagaoka '615 teaches as being the active component. As such, the instant invention is not obvious over Nagaoka '615 and withdrawal of the rejection is respectfully requested.

b) Nagaoka '330 –

Claims 24-27, 30–32 and 34-38 have been rejected under 35 U.S.C.§103 as being obvious over Nagaoka '330. The Examiner similarly asserts that Nagaoka '330 implies or suggests the use of an extract of *Lentinus edodes* mycelium as an anti-tumor extract. Nagaoka '330 is further relied on for teaching the use of an extract of *Lentinus edodes* mycelium for treating viral diseases, such as Hepatitis B and HIV.

Regarding the alleged disclosure in Nagaoka '330 for the anti-tumor activity, the reference contains even less relevant disclosure to the instant invention than Nagaoka '615. The sole disclosure Nagaoka '330 regarding cancer is the recitation in claim 5 that the "viral disease" is liver cancer. Thus, Nagaoka '330 is, in fact, not directed anti-tumor activity but rather anti-viral activity. As with the reasons discussed above regarding Nagaoka '615, there is no suggestion or disclosure in Nagaoka '330 of treating a tumor with the specific extract recited in the claim, through the activation of γδT cell activity.

The indications in Nagaoka '330 for treating viral diseases are readily apparent from the Title, the Abstract and the specification. See for example the "FIELD OF THE INVENTION" which states, "The present invention relates to an inhibitor of Hepatitis B virus and HIV (human immunodeficiency virus) activity." However, the disclosure in Nagaoak '330 regarding the treatment of HIV or hepatitis B is not relevant to the instantly claimed invention of claim 26 and dependent claims thereon, which require efficacy through the enhanced action of γδT cells.

Nagaoka '330 teaches that their extract of Lentinus edodes mycelium has an ability to enhance the activity of the T4 lymphocyte cell line, MT-4. As described in paragraph [0044] of Nagaoka '330, the MT-4 cell line was obtained by modifying human helper T cells with an adult T cell leukemia virus, i.e. MT-4 is an αβT cell. Thus, Nagaoka '330 discloses the activation of αβT cells.

As noted, Nagaoka '330 discloses the activation of αβT cells. However, αβ T cells are completely different from γδT cells with regard to characterization, function etc. One skilled in the art would not consider findings with αβT cells in any way predictive of or relevant to an activity of γδT cells. As such, there is no suggestion of the instant invention in Nagaoka '330 and withdrawal of the rejection is respectfully requested.

2) Nagaoka JP '816 (claims 26-29 and 38)

The Examiner maintains the rejection of 26-29 and 38 under 35 U.S.C. §103 as being obvious over Nagaoka JP '816. In response to Applicants arguments, the Examiner asserts that any *in vivo* effect would be inherent to the composition and therefore is not a patentable feature to the invention. The Examiner further asserts that it would be obvious to use an extract of *Lentinus edodes* mycelium as an anti-bacterial agent, regardless of the mechanism of action.

Claim 26 has been amended, as indicated above, to be directed to a method using oral administration or injection to administer the extract to the patient. Support for the amendment to claim 26 may be found at least in original claims 2 and 7. Nagaoka JP '816 discloses a topically administered cream. Attached hereto is a partial English translation of Nagaoka JP '816, which shows that the only route of administration contemplated in the reference is topical application to treat, for example, "skin roughness, skin irritation, skin sore and skin dryness, to suppress generation of melanin, and to lighten the color of the deposited melanin." See page 1, 3rd paragraph of the partial English translation. Thus, Nagaoka JP '816 discloses only a localized, topical/transdermal administration of the composition.

There is no disclosure or suggestion in Nagaoka JP '816 of oral administration or injection, both of which are systemic administration routes. One skilled in the art would not find teachings regarding a topically administered drug to be in any way predictive or indicative of success with an orally or injection administered, i.e. systemically administered, drug. As such, the invention of claims 26-29 and 38 is in no way suggested by or obvious over the disclosure of Nagaoka JP '816 and withdrawal of the rejection is respectfully requested.

In view of the above Amendments to the claims and Remarks, Applicants believes the pending application is in condition for allowance. If the Examiner has any questions concerning this application, the Examiner is requested to contact MaryAnne Armstrong, Ph.D., Reg. No. 40,069 at the telephone number of (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachments: Partial English translation of Nagaoka JP '816.

EXCERPT TRANSLATION OF THE SPECIFICATION

ABSTRACT

PURPOSE:

A cream composition that contains, as an active ingredient, an extract from mycelia of SHIITAKE mushrooms, thus showing good recovering effect for roughened skins, rash or dried skin and having the action to inhibit the formation of melanin, lighten the color of deposited melanin and the antibacterial action.

CONSTITUTION:

A cream composition that contains an extract from SHIITAKE mushroom mycelia. The extract shows actions not only to inhibit the formation of melanin, but also lighten; the color of melanin. The extract is obtained by inoculating mycelia of SHIITAKE mushrooms in a solid culture medium mainly containing bagasse, loosening the medium, mixing the medium with water, when needed, with enzymes such as protease, extracting crushed solid medium and heating it up to 95 deg.C to effect deactivation of enzymes and sterilization. The extenders into a power and the power is added together with water or an organic solvent to a cream base.

PURPOSE AND SUMMARY (From line 6 of left upper column of page 2 to line 7 of right upper column of page 2):

The present inventor investigated with a view to developing a cream composition which has a superior effect on conditions such as skin roughness, skin irritation, skin sore and skin dryness, to suppress generation of melanin, and to lighten the color of the deposited melanin. As a result of the investigation, the inventor found that an application of a cream composition containing an extract from mycelia of SHIITAKE mushrooms (*Lentinus edodes*) helps rapid recovery from the conditions described above, inhibits a generation of melanin and lightens the color of already deposited melanin. Therefore, the inventor accomplished the invention.

A cream composition of the present invention is characterized by the fact that it contains an extract of *Lentinus edodes* mycelium as a component for inhibiting melanin generation and for improving melanin lightening.

It was found that the cream composition of the present invention is effective for applying to the damaged skin after sunburn.

Further, it was also found that the cream composition of the present invention has a superior anti-microbial property in addition to a recovering effect of the conditions described above and an inhibitory effect of melanin generation.

EFFECT OF THE INVENTION (From lines 1-13 of right upper column of page 3):

The cream composition of the present invention exhibits the following advantageous effect since it contains an extract of *Lentinus edodes* mycelium as an active ingredient:

(a) the present invention can provide a cream composition having an inhibitory effect on the melanin generation or a lightening effect on the color of the already deposited melanin;

(b) the present invention can provide a cream composition having a superior antibacterial action; and

(c) the present invention can provide a cream composition having a superior recovering effect for the conditions such as skin roughness, skin irritation, skin sore and skin dryness.

EXAMPLE 1 (From line 14 of right upper column to line 4 of left lower column of page 3):

A cream composition containing the following components was prepared.

bees wax	10 weight portion
liquid paraffin	50 weight portion
an extract of *Lentinus edodes* mycelium	35 weight portion
benzalkonium chloride solution	0.05 weight portion
pigment, perfume material	moderate amount

The cream composition above was applied to an area of human skin (shoulder) having pigmented spots, which were generated by sunburn, twice a day (in the morning and in the evening) for 4 weeks.

(omitted)

(From the last 2 lines of left upper column of page 4 to line 5 of left upper column of page 5, part of Example 1)

Next, this example exhibits an antimicrobial activity of the extract of *Lentinus edodes* mycelium which is added to the cream composition of the present invention. First, after lyophilizing the extract of *Lentinus edodes* mycelium, which is applied to various species of bacteria, the anti-bacterial ability of the extract of Lentinus edodes mycelium was compared with that of methylparaben. The result is shown in Table 2.

Table 2

Test bacteria	MIC (%)	
	methylparaben	the extract of Lentinus edodes mycelium
C. albicans IFO-1594	0.2	>3
St. aureus 209p	>0.2	1
M. lysodeikticus ATCC 4698	>0.2	0.25
Ps. aeruginosa ATCC 10145	>0.2	0.5
E. coli K-12 OUT 8401	0.025	1
S. typhimurium	0.05	1
Kl. pneumoniae OUT 8017	0.2	1
Ser. marcescens	0.1	1
Asp. niger IFO4407	0.05	>3

Table 2 shows that the cream composition of the present invention exhibits superior anti-bacterial activity.

Further, if the cream composition of the present invention is applied to skin, it is clarified that the cream is free from properties such as skin irritation.

EXAMPLE 2 (From line 6 to the last line of left upper column of page 5):

A cream composition containing the following components was prepared.

paraffin	4.0 weight portion
microcrystalline wax	6.0 weight portion
bees wax	6.0 weight portion
petrolatum (vaseline)	14.0 weight portion
liquid paraffin	42.5 weight portion
sorbitan sesquioleate ester	3.7 weight portion
sorbitan polyoxyethylene monooleate ester (20E.O)	0.8 weight portion
an extract of *Lentinus edodes* mycelium	25.0 weight portion
benzalkonium chloride solution	0.1 weight portion
pigment, perfume material	moderate amount

EXAMPLE 3 (From line 1 to the last line of right upper column of page 5):

A cream composition containing the following components was prepared.

stearic acid	2.0 weight portion

stearin alcohol	7.0 weight portion
reduced lanolin	2.0 weight portion
squalane	5.0 weight portion
octyl dodecanol	6.0 weight portion
polyoxyethylene cetylether (25E.O)	3.0 weight portion
lipophilic glyceryl monostearate	2.0 weight portion
an extract of *Lentinus edodes* mycelium	67 weight portion
propylene glycol	5 weight portion
pigment, perfume material, antioxidizing agent	moderate amount